Systemic venous oxygen saturation after the Norwood procedure and childhood neurodevelopmental outcome

George M. Hoffman, MD,[a,d,f,g] Kathleen A. Mussatto, BSN,[b,c] Cheryl L. Brosig, PhD,[e,g] Nancy S. Ghanayem, MD,[d,g] Ndidiamaka Musa, MD,[d,g] Raymond T. Fedderly, MD,[b,g] Robert D. B. Jaquiss, MD,[c,h] and James S. Tweddell, MD[c,g,h]

Objective: Neonates with hypoplastic left heart syndrome have impaired systemic oxygen delivery and also have a high risk of hypoxic ischemic brain injury with resultant neurodevelopmental impairment. We hypothesized that decreased postoperative oxygen delivery, as measured on the basis of systemic venous oxyhemoglobin saturation, would be related to persistent neurodevelopmental abnormality assessed in childhood.

Methods: Early perioperative hemodynamic data, prospectively acquired from neonates undergoing staged palliation of hypoplastic left heart syndrome by using deep hypothermic circulatory arrest with uniform perioperative management, were tested for relationship to later neurodevelopmental outcome assessed at age 4 years.

Results: Complete hemodynamic and neurodevelopmental data were available in 13 patients aged 7 ± 8 days at the time of the Norwood procedure and aged 4.5 ± 0.7 years at follow-up assessment. The subjects scored significantly below the population mean for motor, visual-motor integration, and composite neurodevelopmental outcomes. The 5 (38%) patients with abnormal outcomes had significantly lower postoperative systemic venous oxygen saturation values than those with normal outcomes (46% ± 8% vs 56% ± 6%, $P = .024$). Standard hemodynamic parameters did not differentiate patient outcomes. The risk of abnormal outcome increased with increasing time at a systemic venous oxygen saturation of less than 40% ($P < .001$). A multivariate model of deep hypothermic circulatory arrest time, systemic venous oxygen saturation, blood pressure, and carbon dioxide tension accounted for 79% of the observed variance ($P < .001$).

Conclusions: Decreased systemic oxygen delivery in the neonatal postoperative period is associated with hypoxic-ischemic brain injury and childhood neurodevelopmental abnormality. Measures of systemic oxygen delivery should be used to guide perioperative strategies to reduce the risk of hypoxic-ischemic brain injury.

From the Departments of Pediatric Anesthesiology,[a] Cardiology,[b] Cardiovascular Surgery,[c] Critical Care Medicine,[d] and Pediatric Psychology,[e] Children's Hospital of Wisconsin, and the Departments of Anesthesiology,[f] Pediatrics,[g] and Cardiothoracic Surgery,[h] Medical College of Wisconsin, Milwaukee, Wis.

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Address for reprints: George M. Hoffman, MD, Anesthesiology and Pediatrics, Children's Hospital of Wisconsin, 9000 W Wisconsin Ave, Milwaukee, WI 53226 (E-mail: ghoffman@mcw.edu).

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Children with congenital heart disease are at increased risk for neurodevelopmental impairment. Causes of reduced neurodevelopmental outcome include genetic factors, abnormalities of the aortic arch (including hypoplastic left heart syndrome [HLHS]),[1] hypoxic-ischemic injury, genetic predisposition,[2] and complex environmental factors.[3-5] Perioperative events are commonly identified as potential causes of hypoxic-ischemic injury,[6-8] particularly prolonged periods of circulatory arrest[9] and other cardiopulmonary bypass (CPB) support strategies that reduce oxygen delivery, such as anemia[10] and alkalosis.[11,12] However, intraoperative factors do not adequately explain all adverse outcomes.[5,8,13-15]

We have previously identified a higher risk of reduced systemic oxygen delivery by using continuous systemic venous oxygen saturation (Svo_2) monitoring and reduced cerebral oxygen saturation by using near-infrared spectroscopy (NIRS) in the early postoperative period in neonates undergoing the Norwood procedure.[15-17]

Positing that impaired neurodevelopmental outcome might be a late manifestation of postoperative hypoxic-ischemic injury, we examined the relationship between neonatal perioperative hemodynamics and school-age neurodevelopmental outcome in survivors of staged palliation of HLHS. The primary hypothesis was that inadequate postoperative oxygen delivery, assessed by measuring Svo_2 after neonatal stage 1 repair, would be a predictor of poor neurocognitive function at age 4 years.

Methods

Patients

All neonates undergoing staged palliation of HLHS since 1996 have had neonatal perioperative hemodynamics maintained in a database. All survivors have been offered enrollment in a neurodevelopmental outcome study after achieving acceptable hemodynamics for completion of the Fontan procedure and attaining a minimum age of 3.5 years. Because perioperative management strategies have evolved over the past decade in ways that might affect hypoxic-ischemic injury, we limited this analysis to patients who had undergone a modified Norwood procedure for stage 1 palliation (S1P) of HLHS or a single-ventricle variant with deep hypothermic circulatory arrest (DHCA) after achievement of synthetic opioid-based perioperative anesthesia, as previously described.[16,18] Cooling to 18°C to 20°C was achieved with a high-flow modified pH-stat strategy with a minimum cooling time of 25 minutes,[19] followed by a shift to alpha-stat blood gas management just before circulatory arrest.[20] All patients had continuous superior vena caval (SVC) Svo_2 monitoring to guide an aggressive inodilator strategy with an Svo_2 target of 50%.[16,18,21]

Of 43 sequential patients who had S1P performed from 1996 through 1999 by using this standardized perioperative management strategy, 30 were alive at the time of this cross-sectional study. Three were excluded because of coexisting anomalies or extreme prematurity thought to independently affect neurodevelopmental performance. Parents of the 27 eligible patients were invited to participate in this study. Responses were obtained from 21 families, and neurodevelopmental testing was completed in 13. Distance greater than 100 miles from the testing center was the primary reason for nonresponse or noncompletion of testing. All patients who had completed neurodevelopmental assessment by September 2004 were included in this analysis.

Neurodevelopment Assessment

A comprehensive test battery was administered by a single developmental psychologist (CLB) under controlled conditions and with institutional review board approval. Individual tests included in this analysis were the McCarthy Scale of Children's Abilities–Motor and the McCarthy Scale of Children's Abilities–General Cognitive, the Beery Test of Visual-Motor Integration, and Achenbach's Child Behavior Checklist. These 4 individual test scores were normalized to an average score of 100 and standard deviation (SD) of 15 and summed to generate a composite outcome score. These tests measure a range of basic and higher-level integrative motor, cognitive, and psychosocial skills, representing areas of function that are at risk for impairment in children with complex congenital heart disease.[9,11,22,23] A cutoff of greater than −2 SD from the population mean was used to classify test results as abnormal.

Hemodynamic Assessment

Perioperative hemodynamic indices were recorded prospectively for the first 48 hours after neonatal S1P, including arterial oxygen saturation (Sao_2), SVC Svo_2, mean arterial blood pressure (MABP), central venous pressure (CVP), heart rate (HR), hemoglobin concentration, $Paco_2$, base excess, and pH and derived parameters of arteriovenous oxygen saturation difference ($Sa\text{-}vo_2$) and arteriovenous oxygen content difference ($Ca\text{-}vo_2$). Intraoperative parameters included duration of support (DHCA time and CPB time) and use of phenoxybenzamine.

Statistical Analysis

Data were expressed as means ± SD for descriptive statistics and as means ± standard error for estimated statistics, with 95% confidence intervals as appropriate. The differences in early hemodynamic parameters between patients with normal or abnormal outcomes were assessed by means of one-way analysis of variance for mean values or by using the Fisher exact test for proportions. The relationship between late outcome and early hemodynamic parameters was assessed by means of multivariate, generalized, least-squares (GLS) time-series regression with correction for autocorrelation and by means of repeated-measures analysis of variance for nonlinear models. Continuous values for hemodynamic parameters were divided into clinically appropriate strata to assess the risk of abnormal outcome at key thresholds by means of binomial odds ratios and time-series logistic regression. The cutoff for significance was a P value of less than .05 after multiple comparison correction with the Tukey honestly significant difference or the Bonferroni method when applicable. All calculations were performed with Stata Version 8 (Stata Corporation, College Station, Tex).

Results

Complete hemodynamic and outcome assessment was available in 13 patients for this analysis. The cohort had S1P at 7 ± 8 days (median, 4 days) at a weight of 3.3 ± 0.7 kg. The duration of DHCA was 62 ± 8 minutes, and the duration of CPB was 128 ± 50 minutes. The postoperative hemodynamic profile was analyzed from a complete set of 624 hours of data. This profile showed a mean Sao_2 of 77% ± 5%, Svo_2 of 52% ± 11%, $Sa\text{-}vo_2$ of 25% ± 9%, hemoglobin concentration of 15 ± 1.5 g/100 mL, $Ca\text{-}vo_2$ of 4.9 ± 1.8 mL/dL, MABP of 52 ± 5 mm Hg, CVP of 11 ± 3 mm Hg, HR of 168 ± 18 min^{-1}, base excess of 3 ± 4 mEq/L, and $Paco_2$ of 41 ± 6 mm Hg. No patients required postoperative mechanical circulatory support.

At the time of neurodevelopment assessment, patients were 4.5 ± 0.7 years of age and ambulatory after completion of the Fontan operation. The study population performed below the population mean on a number of domains. The McCarthy Scale of Children's Abilities–Motor (42 ± 10 vs 50 ± 10, $P = .01$), Beery Test of Visual-motor Integration (87 ± 14 vs 100 ± 15, $P = .006$), and composite

TABLE 1. Summary of neurodevelopmental assessment in the cohort and normal populations

Outcome	Subject score	Population score	No. (%) abnormal	*P* value
MSOCAG	90 ± 27	100 ± 15	3 (23%)	.28
MSOCAM	42 ± 10	50 ± 10	1 (8%)	.01
VMI	87 ± 14	100 ± 15	2 (15%)	.006
CBCL	54 ± 10	50 ± 10	3 (23%)	.18
Composite	352 ± 66	400 ± 50	4 (31%)	.03

Values are presented as means ± SD where shown. *MSOCAG*, McCarthy Scale of Children's Abilities–General Cognitive; *MSOCAM*, McCarthy Scale of Children's Abilities–Motor; *VMI*, Beery Test of Visual-Motor Integration; *CBCL*, Achenbach's Child Behavior Checklist.

TABLE 3. The number of hours spent at different Svo_2 values and relative risk of abnormal composite outcome

Svo_2 (%)	Total (h)	Cases (h)	RR (95% CI)	Exact *P* value
≤30%	23	14	8.5 (4.2-17.1)	<.001
31%-40%	67	28	5.8 (2.9-11.6)	<.001
41%-50%	153	15	1.4 (0.6-3.0)	.523
50%-60%	255	30	1.6 (0.8-3.3)	.21
>60%	125	9	Reference	

Svo_2, Systemic venous oxygen saturation; *RR*, relative risk; *CI*, confidence interval.

scores (352 ± 66 vs 400 ± 60, $P = .03$) were significantly below normal in the cohort. Five (38%; 95% confidence interval, 14%-68%) patients had at least one clearly abnormal score at least 2 SDs below the mean (Table 1).

The patients with any abnormal outcome (n = 5) were grouped to compare their early hemodynamic parameters with those of patients without abnormal outcomes (n = 8). Univariate analysis of hemodynamics showed no significant differences for MABP (51 ± 5 vs 54 ± 3 mm Hg, $P = .23$), Sao_2 (78% ± 3% vs 74% ± 3%, $P = .07$), $Paco_2$ (41 ± 3 vs 39 ± 5 mm Hg, $P = .36$), DHCA time (60 ± 6 vs 67 ± 12 minutes, $P = .18$), CPB time (118 ± 21 vs 150 ± 27 minutes, $P = .33$), or phenoxybenzamine administration (8/8 vs 3/5, $P = .14$) between patients with normal and abnormal outcomes. However, Svo_2 was significantly lower in patients with abnormal outcomes (56% ± 6% vs 46% ± 8%, $P = .024$). Low Svo_2 was present regardless of abnormal outcome assessed (Table 2).

By treating each hour of hemodynamic data as a separate independent "dose," the additive risk of Svo_2 on outcome was assessed in a case-control model. Each hour at an Svo_2 of 40% or less increased the risk of abnormal composite outcome (risk ratio, 4.7; 95% confidence interval, 3.3-6.5; $P < .001$). A clear dose-response effect was present for time at progressively low Svo_2 (Table 3).

Time-series analysis of early hemodynamic parameter patterns showed more subtle influences on late outcomes. In this analysis systemic oxygen delivery, as measured on the basis of Svo_2, Sao_2, and Sa-vo_2, was significantly lower in patients with abnormal outcomes (Figure 1). Borderline differences were observed for $Paco_2$ and MABP (Figure 2). There were no significant differences for hemoglobin concentration, HR, CVP, base excess, or pH (Table 4). Multivariable analysis revealed that the composite outcome score was most powerfully related to circulatory arrest time of greater than 60 minutes, Svo_2, MABP, and $Paco_2$ in a model that explained 79% of the variance in outcome (Table 5). This multivariate predictive model demonstrated a significant nonlinear relationship of Svo_2 to all outcome measures, with an apparent break point at an Svo_2 of less than 40%. The model of composite outcome score versus Svo_2 is shown in Figure 3. Multivariate modeling revealed significant interaction between terms and nonlinear modulation of the Svo_2 effect by $Paco_2$ and prolonged DHCA time (Figures 4 and 5).

Discussion

The main conclusion of this analysis is that systemic oxygen delivery, as assessed on the basis of SVC Svo_2 in the early postoperative period after the Norwood operation, was a significant contributor to neurological function, as assessed

TABLE 2. Postoperative Svo_2 compared according to neurodevelopmental test result

Outcome	No. of subjects abnormal	Svo_2 in subjects with normal outcomes	Svo_2 in subjects with abnormal outcomes	*P* value
MSOCAG	3	54 ± 7	45 ± 11	.08
MSOCAM	1	54 ± 7	34	.014
VMI	2	54 ± 6	39 ± 9	.015
CBCL	2	54 ± 7	41 ± 11	.041
Composite	4	55 ± 6	45 ± 9	.034
Any	5	55 ± 6	46 ± 8	.024

Values are presented as means ± standard deviation where shown. *Svo_2*, Systemic venous oxygen saturation; *MSOCAG*, McCarthy Scale of Children's Abilities–General Cognitive; *MSOCAM*, McCarthy Scale of Children's Abilities–Motor; *VMI*, Beery Test of Visual-Motor Integration; *CBCL*, Achenbach's Child Behavior Checklist.

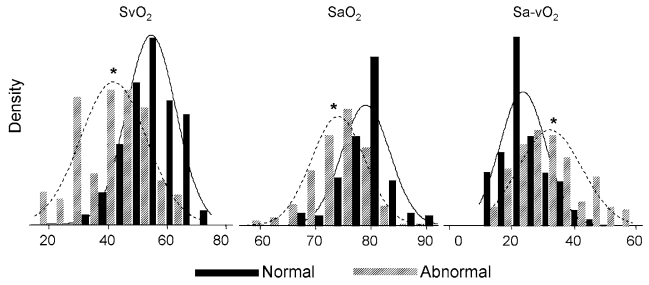

Figure 1. Distributions of systemic venous oxygen saturation *(Svo_2)*, arterial oxygen saturation *(Sao_2)*, and arteriovenous oxygen saturation difference *($Sa\text{-}vo_2$)* over the first 48 postoperative hours in the 2 subgroups of patients. Patients with abnormal outcomes had lower systemic venous oxygen saturation (*P = .012), arterial oxygen saturation (*P = .036), and higher arteriovenous oxygen saturation difference (*P = .039) values.

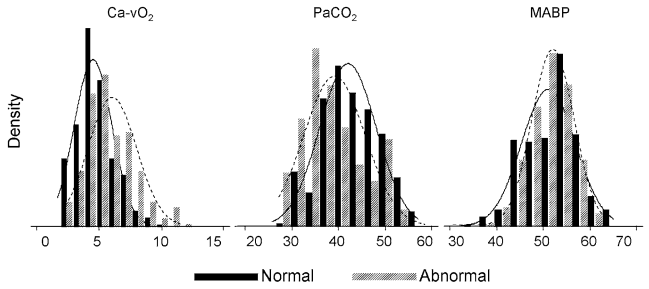

Figure 2. Forty-eight-hour distributions of arteriovenous oxygen content difference *($Ca\text{-}vo_2$)*, $Paco_2$, and mean arterial blood pressure *(MABP)* were not different in patients with normal versus abnormal outcomes.

TABLE 5. Multivariable regression on composite outcome score

Variable	Coefficient	Variance	*P* value	Partial Correlation
DHCA (>60 min)	−99 ± 28	26%	.021	−0.51
Svo_2	5.0 ± 1.6	22%	.031	0.42
MABP	8.3 ± 3.4	21%	.031	0.38
$Paco_2$	8.8 ± 4.4	10%	.011	0.38
Model		79%	.021	

DHCA, Deep hypothermic circulatory arrest; *Svo_2*, systemic venous oxygen saturation; *MABP*, mean arterial blood pressure.

at relatively late follow-up. In this population of children treated at a single institution during a time of little variation in intraoperative and postoperative management, 4 factors (prolonged circulatory arrest time, Svo_2, MABP, and $Paco_2$) accounted for almost 80% of the variance in a composite neurodevelopmental outcome score. Thus this study provides coherent data consistent with the hypothesis that perioperative systemic oxygen delivery can influence neurological function significantly enough to affect long-term development. Although a causal relationship is not proved in this observational study, known pathophysiologic processes link hypoxic-ischemic brain injury with neurodevelopmental delay, and thus management strategies that target improved systemic oxygen delivery might not only improve survival[18,21] but likely also neurologic function.[5,15,24]

The strength of the association between factors related to hypoxic injury and late outcome in this relatively small study results partly from the wide range of performance and frequency of poor performance observed in the subjects' neurodevelopmental testing. The expected probability of 5 abnormal test results in this sample size would be no greater than 1% if drawn from a normal sample. The possibility of selection bias in subjects' participation in neurodevelop-

TABLE 4. Forty-eight-hour hemodynamic profile in patients with normal versus abnormal outcomes

Parameter	Normal outcome (n = 8)	Any abnormal outcome (n = 5)	*P* value
Svo_2 (%)	55 ± 2 (51-60)	46 ± 3 (40-52)	.012
Sao_2 (%)	78 ± 1 (76-80)	75 ± 1 (72-77)	.036
$Sa\text{-}vo_2$ (%)	23 ± 2 (19-26)	29 ± 2 (24-33)	.039
$Ca\text{-}vo_2$ (mL/dL)	4.4 ± 0.4 (3.6-5.2)	5.6 ± 0.5 (4.6-6.6)	.086
POB ($mg \cdot kg^{-1} \cdot d^{-1}$)	0.17 ± 0.04 (0.10-0.24)	0.08 ± 0.05 (0-0.17)	.14
pH	7.42 ± 0.01 (7.39-7.45)	7.45 ± 0.01 (7.42-7.49)	.17
$Paco_2$ (mm Hg)	42 ± 1 (39-45)	39 ± 2 (35-43)	.17
MABP (mm Hg)	51 ± 1 (48-53)	54 ± 2 (50-57)	.18
Hb (g/dL)	14.7 ± 0.4 (14.0-15.4)	14.3 ± 0.5 (13.4-15.1)	.45
CVP (mm Hg)	11.2 ± 1.0 (9.2-13.0)	10.5 ± 1.2 (8.1-12.9)	.67
HR (1/min)	167 ± 4 (159-176)	168 ± 5 (157-179)	.89

Values are presented as means ± standard error (95% confidence interval) where shown. *Svo_2*, Systemic venous oxygen saturation; *Sao_2*, arterial oxygen saturation; *$Sa\text{-}vo_2$*, arteriovenous oxygen saturation difference; *$Ca\text{-}vo_2$*, arteriovenous oxygen content difference; *POB*, phenoxybenzamine; *MABP*, mean arterial blood pressure; *Hb*, hemoglobin; *CVP*, central venous pressure; *HR*, heart rate.

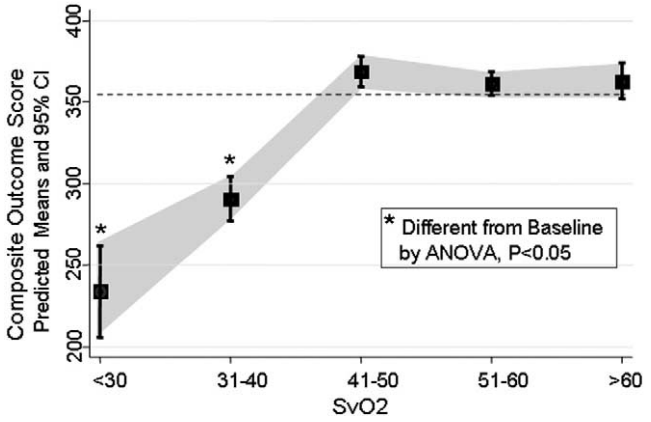

Figure 3. The composite outcome score was modeled as a function of hourly hemodynamic data and cardiopulmonary bypass parameters (arterial oxygen saturation, systemic venous oxygen saturation [Svo_2], mean arterial blood pressure, central venous pressure, $Paco_2$, cardiopulmonary bypass time, and deep hypothermic circulatory arrest time). The model reveals the effect of systemic venous oxygen saturation on outcome, with a break point of a systemic venous oxygen saturation of less than 40% (*$P < .05$, analysis of variance *[ANOVA]*). Adjustment for other parameters did not change the main model effect but increased the power (from $R^2 = 0.49$ to 0.63). *CI,* Confidence interval.

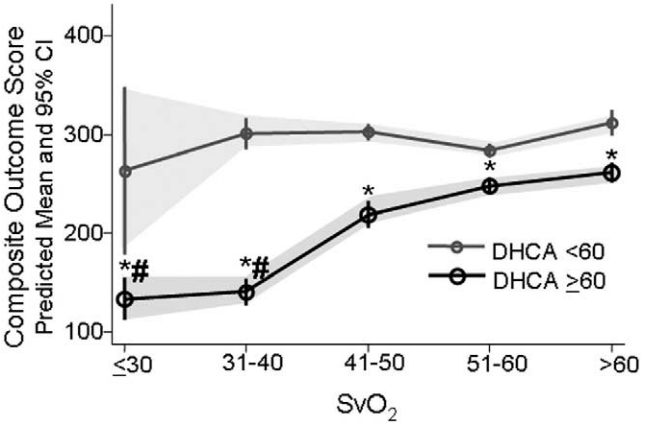

Figure 4. The interaction between prolonged deep hypothermic circulatory arrest *(DHCA)* time and postoperative hemodynamics is shown in a predictive model. Patients undergoing prolonged deep hypothermic circulatory arrest had significantly lower composite outcome scores at low systemic venous oxygen saturation (Svo_2; #$P < .05$, analysis of variance post-tests), and prolonged deep hypothermic circulatory arrest reduced neurodevelopmental outcome for any systemic venous oxygen saturation (*$P < .05$, analysis of variance). Adjustment for other parameters did not change the main or interaction model effects but increased the power (from $R^2 = 0.49$ to 0.58). *CI,* Confidence interval.

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mental assessment might contribute to the incidence of abnormality, but this high incidence is consistent with other reports.[1,3,5,6,23] Although the absolute risk of abnormal outcome could only be estimated by a prospective study with complete ascertainment, the association between low postoperative Svo_2 and poor outcome is not likely to be influenced by ascertainment bias in this sample population. The perioperative demographic and hemodynamic profile of the tested cohort was not different from that of the entire contemporaneously operated S1P population (n = 43, data not shown).

The postoperative hemodynamic parameter most variable in this patient population was Svo_2, but the overall hemodynamic profiles were otherwise distinctly unremarkable. The children with poorer outcomes were specifically not hypotensive, acidotic, or subject to extreme arterial hypoxemia, conditions that have been associated with early postoperative changes on magnetic resonance imaging.[6,25] They received similar levels of inotropic support and had no requirement for cardiopulmonary resuscitation. The results of their management strategy simply failed to achieve the target Svo_2 for a greater period of time. Postoperative mechanical circulatory support was not used on an emergency basis or electively to maintain organ perfusion.[26]

Because standard monitoring modalities did not discriminate patients with abnormal outcomes, we believe that measurements of organ oxygen economy by means of Svo_2 or potentially NIRS should be used to characterize the circulatory vulnerability in these patients and to guide therapy. After S1P, patients are at high risk of inadequate organ

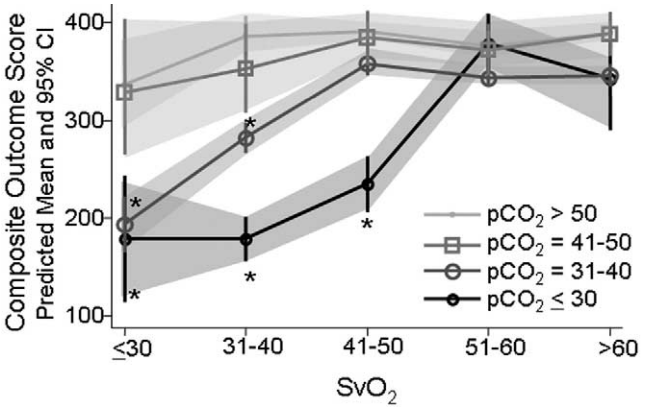

Figure 5. The interaction between postoperative $Paco_2$ and systemic venous oxygen saturation (Svo_2) is shown in a predictive model. Patients with lower postoperative $Paco_2$ had poorer outcome at lower systemic venous oxygen saturation compared with that of patients with higher $Paco_2$ (*$P < .05$, analysis of variance). Adjustment for other parameters did not change the main or interaction model effects but increased the power (from $R^2 = 0.52$ to 0.64). *CI,* Confidence interval.

oxygen delivery and low Svo_2 because of the superimposition of low Sao_2, low systemic blood flow, and increased oxygen consumption.[16,18] However, hypoxic-ischemic organ injury can result from inadequate oxygen delivery from a wide range of conditions, and we believe the relationship between Svo_2 and neurodevelopmental outcome is generalizable to many high-risk populations.

In this relatively small sample, the effect of prolonged DHCA was highly collinear with mild hypocapnia, such that each term had univariate significance, but neither added power to the multivariate model. This finding makes physiologic sense in that prolonged DHCA causes prolonged impairment in cerebrovascular resistance, such that oxygen uptake and carbon dioxide production from the brain are reduced after CPB.[27] The data also support the speculation that a hypercapnic management strategy might improve cerebral blood flow after DHCA through reduction of cerebrovascular resistance.[17,28] The break point for poorer outcome in our sample was DHCA time of greater than 60 minutes compared with the 45-minute break point from the Boston Circulatory Arrest Study.[9] Our CPB strategy maintained a higher Pco_2 and hemoglobin concentration than that in the Boston Circulatory Arrest Study analysis. Strategies that include a higher hemoglobin concentration[10] and a higher $Paco_2$[11] have been shown to improve outcome from DHCA, and thus our data are consistent with a variable dose-dependent injury related to DHCA,[9,22,29] which can be affected by parameters related to cerebral oxygen delivery, such as $Paco_2$ and hemoglobin concentration.

In patients with parallel circulation, reduction in systemic vascular resistance can improve systemic flow by reducing and stabilizing the pulmonary/systemic flow ratio.[30,31] In patients with limited cardiac output, reduction in systemic vascular resistance might divert blood flow away from the cerebral circulation.[17,32] Theoretic objections to the use of afterload reduction in this patient population stem partly from this concern.[33] In this study we found no evidence that the use of phenoxybenzamine impaired neurologic outcome.

The postoperative parameter most strongly related to outcome was Svo_2. Because Svo_2 is the flow-weighted average of regional venous saturations and because the cerebral blood contributes significantly to SVC venous blood in the resting and sedated patient, Svo_2 will be strongly influenced by cerebral oxygen economy.[15,34] The Svo_2 might thus be closely related to whole-brain oxygen saturation in this analysis, and other measures of brain oxygen status, such as NIRS, might more directly reflect conditions of cerebral hypoxia related to adverse outcome.[15,24,35,36]

The hemodynamic vulnerability detected by decreased postoperative Svo_2 reflects impaired oxygen delivery to metabolism balance. This impairment of oxygen economy in the early postoperative period was related to later neurocognitive disability, presumably through the development of hypoxic brain injury. Although low Svo_2 tended to improve over the first 48 postoperative hours, the underlying circulatory vulnerability might persist, and those patients demonstrating late outcome impairment might have recurrent hypoxic injury beyond the acute perioperative period.[5] Strategies to improve Svo_2 and brain oxygenation in the perioperative period and beyond are likely to reduce the occurrence of hypoxic brain injury in high-risk patient populations.

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